WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences

Search Results -

Terms	Documents
l1 and (chromosom$ 14)	161

Database: US Patents Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Refine Search: `l1 and (chromosom$ 14)` Clear

Search History

Today's Date: 10/30/2000

DB Name	Query	Hit Count	Set Name
USPT,DWPI	l1 and (chromosom$ 14)	161	L2
USPT,DWPI	human$ near5 chromosom$	3813	L1

WEST

Generate Collection

Search Results - Record(s) 11 through 20 of 161 returned.

☐ 11. Document ID: US 6096878 A

L2: Entry 11 of 161 File: USPT Aug 1, 2000

US-PAT-NO: 6096878
DOCUMENT-IDENTIFIER: US 6096878 A
TITLE: Human immunoglobulin V.sub.H gene segments and DNA fragments containing the same

L2: Entry 11 of 161 File: USPT Aug 1, 2000

US-PAT-NO: 6096878
DOCUMENT-IDENTIFIER: US 6096878 A
TITLE: Human immunoglobulin V.sub.H gene segments and DNA fragments containing the same
DATE-ISSUED: August 1, 2000

US-CL-CURRENT: 536/23.53; 435/91.1, 536/23.1, 536/23.51

APPL-NO: 8/ 545809
DATE FILED: March 27, 1996

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/JP93/00603	May 10, 1993	WO94/26895	Nov 24, 1994	Mar 27, 1996	Mar 27, 1996

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

☐ 12. Document ID: US 6090924 A

L2: Entry 12 of 161 File: USPT Jul 18, 2000

US-PAT-NO: 6090924
DOCUMENT-IDENTIFIER: US 6090924 A
TITLE: Human-Human CLNH5-specific antibodies

L2: Entry 12 of 161 File: USPT Jul 18, 2000

US-PAT-NO: 6090924
DOCUMENT-IDENTIFIER: US 6090924 A
TITLE: Human-Human CLNH5-specific antibodies
DATE-ISSUED: July 18, 2000

US-CL-CURRENT: 530/388.8; 424/130.1, 424/138.1, 424/141.1, 424/142.1, 424/155.1, 424/174.1, 424/178.1, 424/450, 435/326 , 435/330, 435/344, 435/366, 530/387.1, 530/387.3, 530/388.1, 530/388.15, 530/391.1, 530/391.3

APPL-NO: 8/ 482195
DATE FILED: June 7, 1995

PARENT-CASE:
This application is a continuation of U.S. application Ser. No. 08/443,809, filed May 18, 1995, now abandoned which is a continuation of Ser. No. 08/163,281, filed Dec. 7, 1993, now abandoned, which is a divisional of U.S. application Ser. No. 07/113,212, filed Oct. 23, 1987, now U.S. Pat. No. 5,286,647, which is a continuation-in-part of Ser. No. 06/573,974, filed Feb. 21, 1984 now abandoned, which is a U.S. National Phase of PCT/US83/00781, filed May 20, 1983, which claims priority to Japanese Application No. JP84843-3 and is a continuation-in-part of U.S. application Ser. No. 06/465,081, filed Feb. 9, 1983, which issued as U.S. Pat. No. 4,618,577.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

13. Document ID: US 6083703 A

L2: Entry 13 of 161 File: USPT Jul 4, 2000

US-PAT-NO: 6083703
DOCUMENT-IDENTIFIER: US 6083703 A
TITLE: Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes

L2: Entry 13 of 161 File: USPT Jul 4, 2000

US-PAT-NO: 6083703
DOCUMENT-IDENTIFIER: US 6083703 A
TITLE: Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes
DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 435/6; 435/252.3, 435/252.33, 435/320.1, 435/325, 435/69.3, 536/23.1, 536/23.5

APPL-NO: 9/ 162368
DATE FILED: September 28, 1998

PARENT-CASE:
This is a divisional application Ser. No. 08/725,736 filed Oct. 4, 1998, U.S. Pat. No. 5,831,016, herein incorporated by reference, which is a continuation-in-part application of U.S. application Ser. No. 08/599,602 filed Feb. 9, 1996, U.S. Pat. No. 5,840,839, which is incorporated herein by reference.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

14. Document ID: US 6084087 A

L2: Entry 14 of 161 File: USPT Jul 4, 2000

US-PAT-NO: 6084087
DOCUMENT-IDENTIFIER: US 6084087 A
TITLE: DNA encoding conserved T-cell receptor sequences

L2: Entry 14 of 161 File: USPT Jul 4, 2000

US-PAT-NO: 6084087
DOCUMENT-IDENTIFIER: US 6084087 A
TITLE: DNA encoding conserved T-cell receptor sequences
DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 536/23.5; 530/324, 530/326, 530/330, 536/23.1

APPL-NO: 8/ 963121
DATE FILED: October 28, 1997

PARENT-CASE:
This application is a continuation of application Ser. No. 08/427,009, filed Apr. 24, 1995, now abandoned, which is in turn a division of application Ser. No. 08/229,285, filed Apr. 18, 1994, now abandoned, which is a continuation-in-part of application Ser. No. 07/766,751, filed Sep. 27, 1991 (now U.S. Pat. No. 5,480,895).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

☐ 15. Document ID: US 6080848 A

L2: Entry 15 of 161 File: USPT Jun 27, 2000

US-PAT-NO: 6080848
DOCUMENT-IDENTIFIER: US 6080848 A
TITLE: Human brain associated protein

L2: Entry 15 of 161 File: USPT Jun 27, 2000

US-PAT-NO: 6080848
DOCUMENT-IDENTIFIER: US 6080848 A
TITLE: Human brain associated protein
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 536/23.5; 536/23.1

APPL-NO: 9/ 071434
DATE FILED: May 1, 1998

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

☐ 16. Document ID: US 6077671 A

L2: Entry 16 of 161 File: USPT Jun 20, 2000

US-PAT-NO: 6077671
DOCUMENT-IDENTIFIER: US 6077671 A
TITLE: Method for isolating chromosomal DNA in preparation for hybridization in suspension

L2: Entry 16 of 161 File: USPT Jun 20, 2000

US-PAT-NO: 6077671
DOCUMENT-IDENTIFIER: US 6077671 A
TITLE: Method for isolating chromosomal DNA in preparation for hybridization in suspension
DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 435/6; 435/18, 536/25.4

APPL-NO: 9/ 047175
DATE FILED: March 24, 1998

PARENT-CASE:
This is a continuation of Ser. No. 08/703,302 filed Aug. 26, 1996, now U.S. Pat. No. 5,731,153.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

---

☐ 17. Document ID: US 6074840 A

L2: Entry 17 of 161 File: USPT Jun 13, 2000

US-PAT-NO: 6074840
DOCUMENT-IDENTIFIER: US 6074840 A
TITLE: Recombinant production of latent TGF-beta binding protein-3 (LTBP-3)

L2: Entry 17 of 161 File: USPT Jun 13, 2000

US-PAT-NO: 6074840
DOCUMENT-IDENTIFIER: US 6074840 A
TITLE: Recombinant production of latent TGF-beta binding protein-3 (LTBP-3)
DATE-ISSUED: June 13, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 536/23.5, 536/24.31

APPL-NO: 8/ 479722
DATE FILED: June 7, 1995

PARENT-CASE:
The present application is a continuation-in-part of PCT/US95/02251, filed Feb. 21, 1995; which is a continuation-in-part of U.S. Ser. No. 08/316,350, filed Sep. 30, 1994, now U.S. Pat. No. 5,942,496; which is a continuation-in-part of U.S. Ser. No. 08/199,780, filed Feb. 18, 1994, now U.S. Pat. No. 5,763,416; the entire text and figures of which disclosures are specifically incorporated herein by reference without disclaimer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

---

☐ 18. Document ID: US 6071691 A

L2: Entry 18 of 161 File: USPT Jun 6, 2000

US-PAT-NO: 6071691
DOCUMENT-IDENTIFIER: US 6071691 A
TITLE: Materials and methods for modulating differentiation

L2: Entry 18 of 161 File: USPT Jun 6, 2000

US-PAT-NO: 6071691
DOCUMENT-IDENTIFIER: US 6071691 A
TITLE: Materials and methods for modulating differentiation
DATE-ISSUED: June 6, 2000

US-CL-CURRENT: 435/4; 435/6, 435/7.1

APPL-NO: 9/ 067284
DATE FILED: April 27, 1998

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

☐ 19. Document ID: US 6066459 A

L2: Entry 19 of 161 File: USPT May 23, 2000

US-PAT-NO: 6066459
DOCUMENT-IDENTIFIER: US 6066459 A
TITLE: Method for simultaneous detection of multiple fluorophores for in situ hybridization and multicolor chromosome painting and banding

L2: Entry 19 of 161 File: USPT May 23, 2000

US-PAT-NO: 6066459
DOCUMENT-IDENTIFIER: US 6066459 A
TITLE: Method for simultaneous detection of multiple fluorophores for in situ hybridization and multicolor chromosome painting and banding
DATE-ISSUED: May 23, 2000

US-CL-CURRENT: 435/6; 536/24.3, 536/24.31

APPL-NO: 9/ 100104
DATE FILED: June 19, 1998

PARENT-CASE:
This is a continuation of U.S. patent application Ser. No. 08/635,820, filed Apr. 22, 1996, now U.S. Pat. No. 5,817,462, issued Oct. 6, 1998, which is a continuation-in-part of U.S. patent application Ser. No. 08/575,191, filed Dec. 20, 1995, now U.S. Pat. No. 5,936,731, issued Aug. 10, 1999, which is a continuation-in-part of U.S. patent application Ser. No. 08/571,047, filed Dec. 12, 1995, now U.S. Pat. No. 5,784,162, issued Jul. 21, 1998, which is a continuation-in-part of U.S. patent application Ser. No. 08/392,019 filed Feb. 21, 1995, now U.S. Pat. No. 5,539,517, issued Jul. 23, 1996, which is a continuation-in-part of U.S. patent application Ser. No. 08/107,673, filed Aug. 18, 1992, now abandoned. The specifications of each of these applications are hereby incorporated by reference.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

---

☐ 20. Document ID: US 6060251 A

L2: Entry 20 of 161 File: USPT May 9, 2000

US-PAT-NO: 6060251
DOCUMENT-IDENTIFIER: US 6060251 A
TITLE: Amplification karyotyping

L2: Entry 20 of 161 File: USPT May 9, 2000

US-PAT-NO: 6060251
DOCUMENT-IDENTIFIER: US 6060251 A
TITLE: Amplification karyotyping
DATE-ISSUED: May 9, 2000

US-CL-CURRENT: 435/6; 435/91.2, 435/91.5

APPL-NO: 9/ 124429
DATE FILED: July 29, 1998

PARENT-CASE:
RELATED APPLICATIONS This application is a continuation of application Ser. No. 08/343,358 filed on Nov. 22, 1994, now U.S. Pat. No. 5,869,237, of David C. Ward and Peter Lichter entitled AMPLIFICATION KARYOTYPING which in turn is a File Wrapper continuation application of U.S. Ser. No. 07/960,256 filed on Oct. 13, 1992, now abandoned, which is a File Wrapper Continuation of U.S. Ser. No. 07/577,684 filed Sep. 4, 1990, now abandoned, which is a Continuation-in-part of U.S. Ser. No. 07/271,609 filed Nov. 15, 1988, now abandoned. The contents of all of the aforementioned application(s) are hereby incorporated by reference.

L2: Entry 19 of 161 File: USPT May 23, 2000

DOCUMENT-IDENTIFIER: US 6066459 A
TITLE: Method for simultaneous detection of multiple fluorophores for in situ hybridization and multicolor chromosome painting and banding

BSPR:
The present invention relates in general to a method for simultaneous detection of multiple fluorophores. More particularly, the present invention relates to a spectral imaging method aimed at detecting and analyzing fluorescent in situ hybridizations employing numerous chromosome paints and/or loci specific probes each labeled with a different fluorophore or a combination of fluorophores. Further particularly, the present invention relates to a method of multicolor chromosome banding (i.e., bar-coding), wherein each chromosome acquires a specifying banding pattern, which pattern is established using groups of chromosome fragments labeled with a fluorophore or a combination of fluorophores, this method is referred to herein below also as hybridization based multicolor chromosome banding. The method of the present invention for simultaneous detection of multiple fluorophores is highly sensitive both in spatial and spectral resolutions and is capable of simultaneous detection of dozens of fluorophores and/or combinations of fluorophores, therefore, the method of the present invention can be used for the detection of fluorescently painted complete sets of chromosomes, multiple loci and/or chromosome specific multicolor banding patterns from a species such as human, and to provide a complete multicolor karyotype, wherein each chromosome is identified due to a specifying color, and a complete multicolor chromosome banding pattern, wherein each chromosome is identified according to a specifying multicolor banding pattern.

BSPR:
In a continuation application (U.S. Pat. No. 5,936,731, to Cabib et al., filed Dec. 20, 1995, which is incorporated by reference as if fully set forth herein) the objective was to provide a method for simultaneous detection of multiple fluorophores for detecting and analyzing fluorescent in situ hybridizations employing numerous chromosome paints and/or loci specific probes, each labeled with a different fluorophore or a combination of fluorophores. The method according to this invention is highly sensitive both in spatial and spectral resolutions and is capable of simultaneous detection of dozens of fluorophores and/or combinations of fluorophores, therefore it can be used for the detection of fluorescently painted complete sets of chromosomes and/or multiple loci from a species such as human and to provide a complete color karyotype.

BSPR:
According to still further features in the described preferred embodiments the method is for detecting a trisomy of a genetic material selected from the group consisting of human chromosome 21, human chromosomal band 21q22, a fragment of human chromosomal band 21q22, human chromosome 18, a fragment of human chromosome 18, human chromosome 13 and a fragment of human chromosome 13.

DRPR:
FIGS. 7a, 7b, 7c, 7d and 7e collectively show 24 normalized spectra of 24 pixels of the image of FIGS. 8a and 9a, each of the 24 pixels is derived from a different human chromosome (1-22, X and Y), each of the chromosomes was painted using a different chromosome paint as detailed in Tables 3 and 4 below;

DRPR:
FIGS. 8a and 8b are an RGB image and a color karyotype (presented in black and white) derived from it, respectively, of the 24 human male chromosomes (1-22, X and Y) each of the chromosomes was painted using a different chromosome paint as

detailed in Tables 3 and 4 below, obtained using the method of the present invention;

DRPR:
FIGS. 10a, 10b, 10c and 10d are (a) an RGB image, (b) a color karyotype derived from it, (c) a classification mapping of the image under a, and (d) a color karyotype derived from c, respectively, of the 24 human male chromosomes (1-22, X and Y) each of the chromosomes was painted using a different chromosome paint as detailed in Tables 3 and 4 below, obtained using the method of the present invention, all images are presented in black and white.

DRPR:
FIG. 18 is a multicolor spectral karyotype of the gibbon species Hylobates concolor after hybridization with human chromosome painting probes;

DRPR:
FIG. 22a, 22b and 22c are (a) a R-banding image using DAPI for chromosome staining, (b) a G-banding image obtained presenting the negative image of FIGS. 22a, and (c) a color karyotype RGB image using human chromosome paints of a single mouse chromosome spread, all obtained using the SpectraCube.TM. system.

DEPR:
The present invention is of a spectral imaging method for detecting and analyzing fluorescent in situ hybridizations employing numerous chromosome paints, chromosome fragments and loci specific probes labeled with different fluorophore or a combination of fluorophores, the method is highly sensitive both in spatial and spectral resolutions and is capable of simultaneous detection of dozens of fluorophores or combinations of fluorophores. Therefore, the method of the present invention can be used for detection of fluorescently painted complete sets of chromosomes, multiple loci and/or chromosome specific multicolor banding (i.e., bar-coding) patterns from a species such as human, and to provide a complete multicolor karyotype, wherein each chromosome is identified due to a specifying color and a complete multicolor chromosome banding pattern, wherein each chromosome is identified according to a specifying multicolor banding pattern.

DEPR:
More than 5,000 genetic disorders have now been identified, many of which are associated with multiple genetic defects. After the discovery that chromosomes are the carriers of hereditary information, scientists reasoned that it should be possible to document visible defects in chromosomes that were responsible for specific disorders. In the 1960's, staining techniques were developed for microscopy-based classification of metaphase chromosomes spread onto glass slides. For several decades, visual analysis of chromosomes banding patterns has been used to correlate human genetic disorders with observed structural abnormalities in metaphase chromosomes. Chromosomes are typically examined by brightfield microscopy after Giemsa staining (G-banding), or examined by fluorescence microscopy after fluorescence staining (R-banding), to reveal characteristic light and dark bands along their length. Careful comparison of a patient's banding pattern with those of normal chromosomes can reveal abnormalities such as translocations (exchange of genetic material between or within chromosomes), deletions (missing chromosomes or fragments of chromosomes), additions, inversions and other defects that cause deformities and genetic diseases.

DEPR:
For example, if chromosome A is specifically labeled with a green paint and chromosome B is labeled with a red paint, any translocation of genetic material from A to B will appear as a green area on a red chromosome (and vice versa). Typically, chromosome paints generated from normal chromosomes are used to detect deletions or translocations on abnormal (patient) chromosomes. Reverse chromosome painting uses probes generated from an abnormal chromosome to identify DNA from various normal chromosomes which contributed material to the abnormal chromosome. The method of the present invention, as exemplified hereinbelow in the Examples section, enables to paint the 24 different chromosomes comprising the human karyotype (i.e., genome) each in a different color and simultaneously detect, identify and meaningfully display a color human karyotype, using a single hybridization followed by a single measurement.

DEPR:
The first goal of the human genome project (HGP) is about to be completed. This goal is the generation of a physical map of the human genome. The term physical map refers to the cloning of the entire genome in large insert vectors such as YAC-clones or BAC-clones and the mapping of these clones by means of genetic, cytogenetic and physical mapping. Two major sources of human DNA were used for this endeavor, radiation hybrid cell lines and YAC-contigs that contain overlapping clones for all human chromosomes. The completion of this map allows to retrieve for virtually every region in the genome specific clones that are required to identify genes that are causally involved in inherited or acquired genetic diseases including cancer. By combining FISH with multiple YAC- or BAC-clones or radiation hybrids and spectral imaging it is possible to generate a multicolor banding pattern for all human chromosomes that will ultimately link the genetic and the cytogenetic map.

DEPR:
As an example, consider the use of a radiation hybrid panel (Stanford panel) [see, Barret J. H. (1992) Genetic mapping based on radiation hybrids. Genomics 13, 95-103]. Each individual panel of the Stanford panel contains a set of DNA fragments with an average fragment size of ca. 5,000 Kbp. Each individual panel covers ca. 20% of the human genome. The cohyhridization of fluorescent probes derived from five such panels would therefore result in coverage of most of the genome and thus labeling of all human chromosomes. However, the fragments are randomly distributed in the individual panels. Therefore, the number of panels that are required for a complete coverage of the human genome is higher (e.g., 6-10 panels).

DEPR:
It is also conceivable that such a multicolor banding pattern could be readily automated. Despite considerable efforts automation of cytogenetic diagnosis based on conventional chromosome bands was so far not successful. The approach described hereinabove will not only be applicable for the generation of a hybridization based banding pattern of human chromosomes but also for other mammalian (e.g., mouse) and non-mammalian species. This will be particularly useful for the analysis in animal models of human diseases including cancer.

DEPR:
In analogy to the scenario described for the radiation hybrid panels, a multicolor banding pattern for all human chromosome could be achieved by cohybridization of a set on individual large insert clones such as YAC-clones, P1-clones, BAC-clones or, depending on the resolution that is desired the use of contigs (overlapping clones) from these sources. In further analogy to the use of radiation hybrid panels, a multicolor banding pattern could be introduced by deliberately labeling overlapping clones or contigs with different fluorophores. All advantages of the hybridization based chromosome banding approach has as compared to the use of chromosome paints or to conventional chromosome banding described above, applies to usage of large inserts clones as well. It will be appreciated by one ordinarily skilled in the art that the retrieval of clones involved in chromosome breakpoints or in chromosomal deletion would be even more straightforward than with the use of radiation hybrid panels.

DEPR:
Probes that are useful in the attempts to generate a multicolor banding pattern off the entire chromosome complement (i.e., genome) are either microdissection libraries that contain chromosome band specific sequences, YAC (or other) contigs, radiation induced hybrid cell lines with a specific and known representation of human sequences or large chromosome fragments generated by endonuclease digestion followed by PFGE size separation, that produce a fixed multicolor banding pattern along all chromosomes. The change in the color pattern would indicate, with high resolution, the presence of chromosomal aberration(s). It is clear that such an approach is highly flexible in its design, and could be easily automated.

DEPR:
The generation of a multicolor banding pattern of chromosomes (i.e., multicolor banding karyotype) and chromosome painting based on FISH and spectral imaging, can be used for various additional applications. These include for example (i) biological dosimetry, wherein screening of metaphase plates from individuals exposed to radiation or chemicals known to induce chromosomal aberrations is

performed to establish damages; (ii) chromosome evolution, wherein FISH is used to reconstruct chromosomal rearrangements that occurred during evolution; (iii) the analysis of chromosomal aberrations in animal models of human diseases, in particular cancer, would be greatly facilitated using hybridization based karyotyping; (iv) interphase cytogenetics, wherein the simultaneous enumeration of chromosome copy number in intact interphase cells has application for the detection of aneuploidies in prenatal diagnosis and in cancer research and diagnostic of minimal residual diseases, in combination with confocal laser scanning microscopy this would become a splendid research tool for the analysis of the architecture of the interphase chromatin; (v) cytological diagnosis, wherein complementation of histochemical diagnosis by using multiprobe FISH directly on tissue section and nucleus, possibly in combination with confocal laser scanning microscopy or deconvolution algorithms.

DEPR:
According to the method for hybridization based multicolor chromosome banding, the chromosome fragments may be of any suitable source. Preferably the fragments are derived from radiation hybrid cell lines such as human-hamster radiation hybrid cell lines, YAC-clones (e.g., contigs), BAC-clones, size separated endonuclease digestion products of a complete genome of a selected species or and microdissected chromosome fragments from that species. Yet other sources of chromosome fragments such as ones obtained by gradient centrifugation may be employed to implement the method of the present invention. Collectively the fragments may cover any fraction of the genome. Examples include a 10-20%, 21-30%, 31-40%, 41-50%, 51-60%, 61-70%, 71-80%, 81-90% and coverage. The method is preferably exercised on the human species, yet any desired species (e.g., mouse) may be the subject of analysis according to the method. Furthermore, the method may be exercised in an interspecies fashion wherein the chromosomes are from a first species (e.g., mouse, monkey, etc.) and the chromosome fragments are from a second species (e.g., human). In a preferred embodiment the chromosome fragments are grouped into groups, each of the groups is labeled with a different fluorophore or combination of fluorophores. Labeling of the chromosome fragments may be achieved by for example IRS-PCR such as Alu-PCR if the fragments are from human.

DEPR:
Hybridization takes place at 37.degree. C. Certain probes, however, need higher hybridization temperatures. This applies in particular to repetitive DNA probes in order to ensure their chromosome specificity (alternatively, the stringency can be increased by decreasing the salt concentration in the hybridization solution, e.g. to 0.5.times.SSC final). Since during hybridization the coverslips are sealed with rubber cement, a moist chamber is not required. A hybridization time of 12 to 16 hours is sufficient for all locus specific probes, i.e., cosmid probes or phage clones. Chromosome painting is also done overnight, however, if chromosomes of distant species are to be painted with human probes, longer hybridization times (and higher probe concentrations) are preferred. When entire genomes are hybridized (e.g., CGH) the hybridization time is extended to 2 to 4 days.

DEPR:
the present invention to measure and analyze multiple spectrally overlapping labeled probes (single and combinatorial). In this Example, spectral bio-imaging which, as delineated above, is a combination of Fourier spectroscopy, CCD-imaging and optical microscopy enabling the measurement of definitive spectral data simultaneously at all points of a biological sample, was used to visualize hybridization based multicolor appearance of all (i.e., 24) types of human chromosomes and to generate a color map of the human karyotype.

DEPR:
For this purpose, 24 chromosome paints (1 through 22, X and Y, Table 4) each labeled with a different combination of five or less different flourophores according to the combinatorial hybridization approach (a through e, Table 3), (see Table 3 for the different fluorophores and their spectral characteristics and Table 4 for the assignment of the fluorophores listed in Table 3 to obtain the 24 chromosome paints), were simultaneously hybridized with human mitotic chromosome spreads of two non-related male white blood cells, prepared for hybridization essentially as described in Ried et al. [Ried et al., (1992) Simultaneous visualization of seven different DNA probes by in situ hybridization using combinatorial fluorescence and digital imaging microscopy. Proc. Natl.

Acad. Sci. USA 89, 1388-1392]. Hybridized chromosomes were viewed through an inverted fluorescence microscope connected to the SpectraCube.TM. System and were analyzed.

DEPR:
With reference now to FIGS. 7a-e, 8a-b and 9a-b. FIGS. 7a-e show normalized spectra of 24 individual pixels, each of a different type of human chromosome (1-22, X and Y). Numbers 1-22 and letters X and Y, refer to the chromosome type of which each of the spectra presented were derived. Note that the spectrum obtained from each of the 24 human chromosomes, as shown in FIGS. 7a-e, differ from all other spectra. This difference may be large (compare, for example, the Ca. 530 nm emission peak of chromosome 15 and 11 in FIG. 7c) or small (compare, for example, the Ca. 530 nm emission peak of chromosome 22 and Y in FIG. 7e) and, in some spectral ranges may even disappear (compare, for example, the Ca. 680 nm emission peak of chromosome 22 and Y in FIG. 7e). Nevertheless, as further shown in FIGS. 7a-e, even a minor difference between very similar spectra can be detected using the SpectraCube.TM. system and the method of the present invention. It is however clear from this description that the ability of the method of the present invention to detect differences among spectra, to a large extent depends upon appropriate fluorophores and fluorophore combinations selected, yet, as will be appreciated by one ordinarily skilled in the art and even by one expert in the art, the ability herein demonstrated, far beyond exceeds that of any prior art cytogenetic technique.

DEPR:
FIG. 8a shows an RGB image of thus described painted human chromosomes, whereas FIG. 8b shows a color human karyotype derived from the painted chromosomes of FIG. 8a. Since it is not possible to literally describe 24 different colors, colored FIGS. 9a and 9b which are otherwise identical to black and white FIGS. 8a and 8b, respectively, are also enclosed. Note that each of the chromosome pairs is painted in a different color and that the color karyotype (FIG. 9b) is readily derived from the color image (FIG. 9a).

DEPR:
With reference now to FIGS. 10a-d and 11a-d. FIG. 10a shows an RGB image of painted human chromosomes of another individual, whereas FIG. 10b shows a color human karyotype derived from the painted chromosomes of FIG. 10a. FIGS. 10c and 10d show a classification map of the painted human chromosomes and derived karyotype of FIGS. 10a and 10b, respectively. Since it is very difficult to literally describe 48 different colors and shades, colored FIGS. 11a-d which are otherwise identical to black and white FIGS. 10a-d, respectively, are also enclosed. Note that each of the chromosome pairs is painted in a different color and that the color karyotypes are readily derived from the color images, both for RGB and classification mapping algorithms.

DEPR:
In this Example, the use of 24 different single and combinatorial probes combined from five different basic fluorophores as prepared according to the combinatorial hybridization approach (a through e, Table 3) was demonstrated for human color chromosome karyotyping. Nevertheless, some other species have a greater number of chromosomes, which perhaps requires the use of more complicated combinatorial probes combined of more basic fluorophores. Yet, it should be noted that chromosomes, including human chromosomes, can also be classified to size groups, which, for some applications minimize the need for as many different colors since chromosomes belonging to different size groups may be similarly colored yet easily recognized according to their relative size. This could be achieved by manual inspection, or alternatively using any morphological algorithm. It is however clear to one ordinarily skilled in the art that other algorithms may equivalently or better suit the purpose of displaying similar images.

DEPR:
With reference now to FIGS. 12a-e, 13a-e 14 and 15. Chromosome spreads of breast cancer cell line SKBR3 were hybridized with the 24 chromosome paints (1 through 22, X and Y) as detailed in tables 3 and 4 above and were spectrally imaged as detailed under Example 2 above. FIGS. 12a and 13a and FIGS. 12c and 12d show DAPI R-banding of two chromosome spreads as was photographed using a conventional fluorescence microscope (12a, 13a) and as was imaged using the SpectraCube.TM. system with a DAPI filter (i.e., DAPI band pass filter cube) (12c, 13c). It will be appreciated that although the resulting karyotype as depicted from these

Figures is abnormal to a large extent, it is impossible to identify specific translocations of chromosomes. FIGS. 12b and 13b and FIGS. 12d and 13d show (in black and white and color, respectively) RGB images of the same spreads as was obtained using the SpectraCube.TM. system and the method of the present invention. When compared with FIGS. 9a-b, presenting a normal human karyotype derived under otherwise identical experimental conditions, it is apparent that many of the aberrations containing chromosomes shown in FIGS. 12b and 13b contain parts of various normal human chromosomes. The translocated chromosomes (right) of FIGS. 12b and 13b, along with the R-banded chromosomes (left) are shown in FIGS. 14 and 15. Note that some of the translocated chromosomes shown in FIGS. 14 and 15 include fragments originated from two, three and even four different chromosomes. Further note that large stretches of chromosomal material is painted with the chromosome 8 paint, suggesting increased copy number for this chromosome.

DEPR:
In addition to diagnostic applications in clinical and cancer cytogenetics as described above in examples 3 and 4, spectral karyotyping according to the method of the present invention is a versatile research tool for comparative cytogenetics [see, J. Weinberg and R. Stanyon (1995) Current opinion in genetics and development 5, 792-797]. Rearrangements which changed chromosome morphology during evolution can readily be visualized. For example, with reference now to FIGS. 18 and 19, using the human chromosome painting probes of Example 2, it was possible to reconstruct the highly rearranged karyotype of a gibbon species in a single hybridization. Thus, FIGS. 18 and 19 present a spectral karyotype of the gibbon species Hylobates concolor after hybridization with human painting probes. Note that the gibbon X-chromosome is entirely painted with the human X-chromosome. Most of the autosomes e.g., chromosomes 19, reveal a banding pattern reflecting multiple evolutionary chromosomal rearrangements.

DEPR:
In the study of evolutionary related species and in the study of model systems (for example mouse as a model system for human) it is in many cases required to obtain comparative genome maps in which chromosomes of two or more species are aligned according to their sequence similarities and thus their chromosome-borne genetic information. Using the method of the present invention will facilitate obtaining such comparative maps. Consider for example the preparation of a human-mouse chromosome comparative map. For this purpose a complete set of chromosome paints of one of the species (e.g., human) are to be simultaneously hybridized with chromosome spreads of the other species (mouse in the given example) and analyzed as described above. The result is an image of the mouse karyotype painted with the human chromosome paints. Thus, an alignment can be made between the karyotypes of the two species.

DEPR:
The bar codes shown in human chromosomes 5, 2, 10, 13, 16 and 7 were created using fluorescently labeled radiation hybrid chromosome fragments (for 5, 2, 10, 13 and 16) or YAC-clones (for 7) as a source for multi color chromosome fragments.

DEPR:
The color bar code along the short arm of chromosome 7 was created using six different YAC-clones previously mapped close to one another at known locations onto the short arm of human chromosome 7. These six YAC-clones were labeled with the above mentioned green and red fluorophores, in an alternating fashion according to their known chromosomal positions. The colors shown in the RGB image obtained were similarly chosen using a suitable RGB look-up-table for enhancing the result. Please note six different bars along the chromosome, each represents the hybridization of a different clone. As opposed to the above description concerning chromosomes 5, 2, 10, 13 and 16, in this case (i.e., chromosome 7), one can predict the banding pattern associated with the given chromosome, by selecting hybridization probes of known chromosomal origin.

DEPR:
For G- or R-banding mouse chromosomes where stained with DAPI. For color karyotyping the DAPI stained chromosomes were thereafter hybridized with a complete set of human chromosome paints, as detailed under Tables 2 and 3 above. In order to achieve optimal spatial resolution, the objective used to acquire the DAPI images was x100 and the triple filter cube typically used for color

karyotyping was replaced with a special DAPI band pass filter cube (excitation 350-400 nm, emission 400-450 nm). Such a filter cube is very common and exist for each microscope type and manufacturer. Then, by moving the scanner rapidly back and forth continually, the image was measured in an exposure time of about 5-15 seconds. The reason for moving the scanner as described was to eliminate fringes and to obtain clearer images. The relatively long exposure time is needed because usually the intensity of the DAPI dye is much less than that of the other fluorescent dyes. On the other hand DAPI is a stable fluorophore and does not bleach during time to the extent of other fluorophores such as ones used for color karyotyping. Obtained is a gray level image of DAPI R-banding (FIGS. 22a and 23a). In order to extract most of the information out of the DAPI R-banding image, the negative image was calculated, yielding the G-banding pattern which is more familiar to cytogeneticists (FIGS. 22b and 23b). This was done by using an invert function of the general form: I'.sub.x,y =N-I.sub.x,y, where N is the maximal dynamic range of the camera (in this case N=4,095), I is the positive intensity at each x,y location and I' is the calculated negative intensity at each x,y location. The result can be farther improved by enhancing the gray levels look-up-table.

DEPR:
The color karyotype image of the same chromosome spread was also measured and is presented in FIGS. 22c and 23c. It can be clearly observed that the correlation of those images can lead to a high accuracy of chromosome identification. It will be appreciated that it is much harder to identify mouse chromosomes as compared with human chromosomes since they are more uniform in size and are less specifically banded using conventional chromosome banding techniques. As a result few scientists are capable of identifying mouse chromosomes. Nevertheless, using the color karyotyping and/or the multicolor banding method of the present invention, identifying

DEPC:
SIMULTANEOUS VISUALIZATION OF ALL HUMAN CHROMOSOMES IN DIFFERENT COLORS USING FLUORESCENT IN SITU HYBRIDIZATION, SPECTRAL BIO-IMAGING AND RGB ALGORITHM

DETL:
TABLE 4

Flourophores	Chromosome	Chromosome paint
human chromosome	1	1 b,c,d
human chromosome	2	2 a,d,e
human chromosome	3	3 a,c,e
human chromosome	4	4 a,c,d
human chromosome	5	5 a,b,e
human chromosome	6	6 a,b,d
human chromosome	7	7 b,c,e
human chromosome	8	8 a,b,c
human chromosome	9	9 d,e
human chromosome	10	10 c,e
human chromosome	11	11 c,d
human chromosome	12	12 b,e
human chromosome	13	13 b,d
human chromosome	14	14 b,c
human chromosome	15	15 a,e
human chromosome	16	16 a,d
human chromosome	17	17 a,c
human chromosome	18	18 a,b
human chromosome	19	19 e
human chromosome	20	20 d
human chromosome	21	21 c
human chromosome	22	22 b
human chromosome	X	X c,d,e
human chromosome	Y	Y a

CLPR:
8. A method as in claim 7, wherein said method is for detecting a trisomy of a genetic material selected from the group consisting of human chromosome 21, human chromosomal band 21q22, a fragment of human chromosomal band 21q22, human chromosome 18, a fragment of human chromosome 18, human chromosome 13 and a fragment of human chromosome 13.

ORPL:
Schrock et al. "Multicolor Spectral Karyotyping of Human Chromosomes", Science,273: 494-497, 1996.

ORPL:
Speicher et al, "Karyotyping Human Chromosomes by Combinatorial Multi-Fluor FISH", Nature Genetics, vol. 12, 1996.

L2: Entry 19 of 161 File: USPT May 23, 2000

US-PAT-NO: 6066459
DOCUMENT-IDENTIFIER: US 6066459 A
TITLE: Method for simultaneous detection of multiple fluorophores for in situ hybridization and multicolor chromosome painting and banding
DATE-ISSUED: May 23, 2000

US-CL-CURRENT: 435/6; 536/24.3, 536/24.31

APPL-NO: 9/ 100104
DATE FILED: June 19, 1998

PARENT-CASE:
This is a continuation of U.S. patent application Ser. No. 08/635,820, filed Apr. 22, 1996, now U.S. Pat. No. 5,817,462, issued Oct. 6, 1998, which is a continuation-in-part of U.S. patent application Ser. No. 08/575,191, filed Dec. 20, 1995, now U.S. Pat. No. 5,936,731, issued Aug. 10, 1999, which is a continuation-in-part of U.S. patent application Ser. No. 08/571,047, filed Dec. 12, 1995, now U.S. Pat. No. 5,784,162, issued Jul. 21, 1998, which is a continuation-in-part of U.S. patent application Ser. No. 08/392,019 filed Feb. 21, 1995, now U.S. Pat. No. 5,539,517, issued Jul. 23, 1996, which is a continuation-in-part of U.S. patent application Ser. No. 08/107,673, filed Aug. 18, 1992, now abandoned. The specifications of each of these applications are hereby incorporated by reference.